Docket No.: 2002.750US
(PATENT)

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Patent Application of:
Cornelis Marius Timmers

Application No.: 10/540,336 Confirmation No.: 8846

Filed: January 10, 2006 Art Unit: 1625

For: TETRAHYDROQUINOLINE DERIVATIVES Examiner: David K. O'Dell

DECLARATION UNDER 37 C.F.R. § 1.132

I, CORNELIS MARIUS TIMMERS, of Boterbloem 26, 5351 MV, Berghem, The Netherlands, declare as follows:

I. BACKGROUND

1. I am a named co-inventor of U.S. application Serial No. 10/540,336 ("the '336 application") filed January 10, 2006.

2. I received my PhD degree in 1997 from Leiden University, The Netherlands. Since 1997, I have worked for Organon as (senior) research scientist. I am currently Organon's senior director Lead Optimization. In that position, I am responsible for providing medicinal chemistry support to various project teams in Lead Optimization.

3. I have reviewed and understood the specification and claims of U.S. patent application Serial No. 10/540,336 entitled "Tetrahydroquinoline Derivatives".

II. TETRAHYDROQUINOLINE DERIVATIVES OF TO THE PRESENT APPLICATION

4. I have carefully reviewed the examples in the application describing the preparation of tetrahydroquinoline derivatives.

5. I have carefully reviewed the method of determining CHO-FSH bioactivity as described in the specification of the present application and as set forth in Example 51 of the specification.

6. The attached table accurately reflects the chemical structure of each of the 50 examples and the bioactivity for each of these examples as obtained at the time the present application was filed. The term "FSH_AGOCHO EC50" in the table reflects the EC50 value for agonist activity of the particular compound with respect to the FSH receptor which is expressed in CHO cells for the assay described in Example 51 of the specification. The term "FSH_ANTCHO EC50" in the table reflects the EC50 value for antagonist activity of the particular compound with respect to the FSH receptor which is expressed in CHO cells for the assay described in Example 51 of the specification.

7. An EC50 value of less than 1.00E-5 for FSH_AGOCH indicates that the particular compound in the table is considered to have agonist activity. An EC50 value of less than 1.00E-5 for FSH_ANTCHO indicates that the particular compound in the table is considered to have antagonist activity. Some compounds in the table have an EC50 value of less than 1.00E-5 for both FSH_AGOCHO and for FSH_ANTCHO and these compounds are considered to have both agonist activity and antagonist activity at different concentrations of the particular compound.

III. CONCLUSION

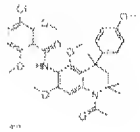
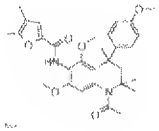
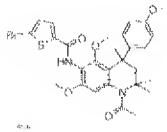
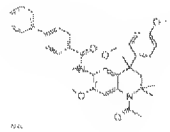
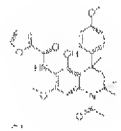
8. In summary, the attached table provides both structural information and bioactivity data for each of the compounds of examples 1 to 50 of the present application. These compounds are exemplary for the class of compounds described by formula I as in the present application and show either agonist activity, antagonist activity or both with respect to the FSH receptor according to the assay described.

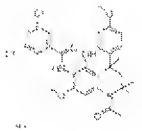
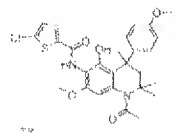
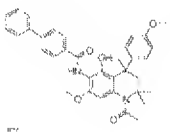
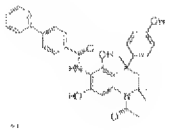
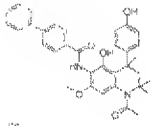
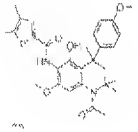
9. I declare that all statements made herein are true, and that all statements made herein on information and belief are believed to be true, and that all statements are made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment or both under Section 1001 of Title 18 of the United States Code, and that any willful false statement may jeopardize the validity of any United States Patent that would issued from the '535 application.

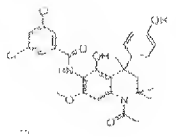
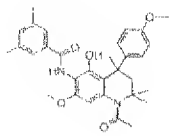
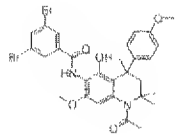
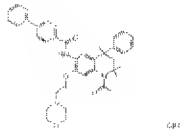
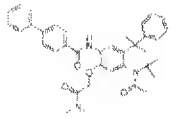
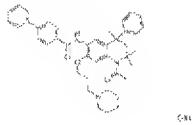
Dated: 19 May 2008 Signed: _____

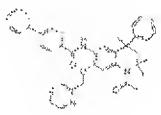
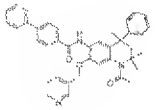
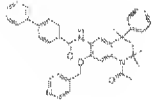
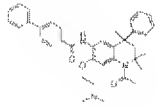
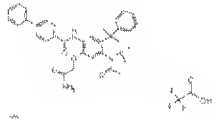
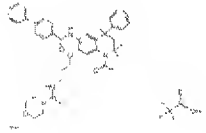
Cornelis Marius Timmers

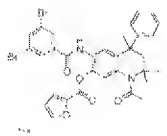
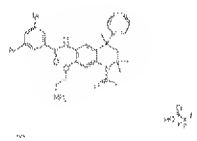
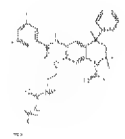
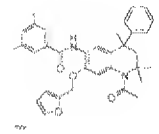
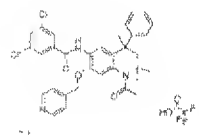
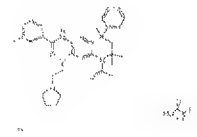
TABLE 1

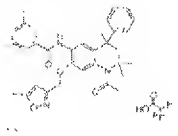
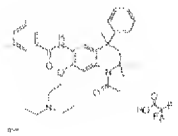
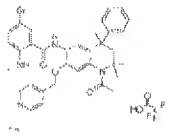
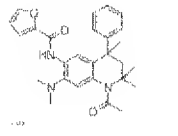
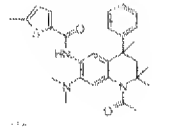
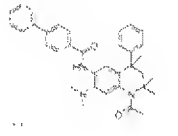
Ex#	COMMON STRUCTURE	FSH_ AGOCHO EC50	FSH_ ANTCHO EC50	R1,R2	R3	R4	R5	R6	R7	R8	R9
1		2.70E-06	> 1.000E-05	Me	OMe	OMe	OMe	diMeOClPh			
2		> 1.00E-05	2.678E-07	Me	OMe	OMe	OMe	diMe-2-furyl			
3		> 1.00E-05	1.904E-07	Me	OMe	OMe	OMe	Br-thiophenyl			
4		> 1.00E-05	4.455E-07	Me	OMe	OMe	OMe	biphenyl			
5		> 1.00E-05	3.914E-08	Me	OMe	OH	OMe	furyl			

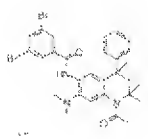
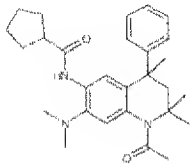
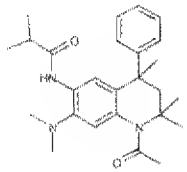
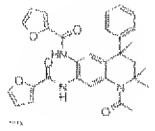
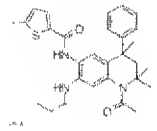
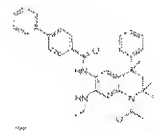
6		9.08E-08	> 1.000E-05	Me	OMe	OH	OMe	diClPh
7		> 1.00E-05	1.390E-08	Me	OMe	OH	OMe	Cl-thiophenyl
8		> 1.00E-05	3.900E-08	Me	OMe	OH	OMe	biphenyl
9		> 1.00E-05	1.257E-07	Me	OH	OH	OH	biphenyl
10		> 1.00E-05	6.036E-09	Me	OH	OH	OMe	biphenyl
11		3.40E-07	5.10E-08	Me	OMe	OH	OMe	4,5-dimethylfuranyl

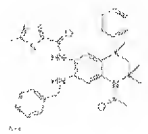
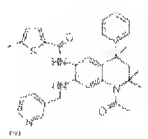
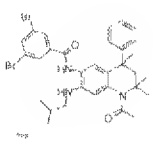
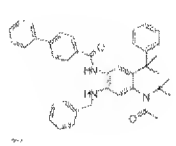
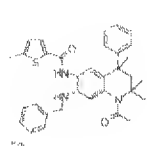
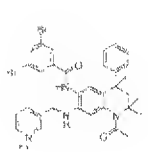
12		3.10E-08	>1.0e-5	Me	OH	OH	OMe	3,5-dichlorophenyl			
13		2.50E-08	>1e-5	Me	OMe	OH	OMe	3,5-dimetylphenyl			
14		2.10E-08	>1.0e-5	Me	OMe	OH	OMe	3,5-dibromophenyl			
15		> 1.00E-05	2.564E-07	Me	H	H	R7	biphenyl	R8-ethoxy	morpholino	
16		> 1.00E-05	3.612E-08	Me	H	H	R7	biphenyl	R9-methoxy		dimethyl amino carbonyl
17		> 1.00E-05	5.088E-06	Me	H	H	R7	biphenyl	R8-propoxy	piperidinyl	

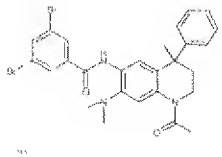
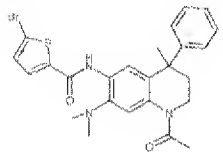
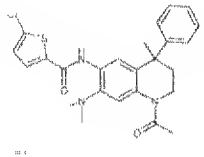
18		> 1.00E-05	1.591E-08	Me	H	H	R7	biphenyl	R9-methoxy		2-pyridinyl
19		> 1.00E-05	1.316E-08	Me	H	H	R7	biphenyl	R9-methoxy		3-pyridinyl
20		8.80E-08	>e-5	Me	H	H	R7	biphenyl	R9-methoxy		4-pyridinyl
21		> 1.00E-05	2.383E-07	Me	H	H	R7	biphenyl	R8-ethoxy	dimethylamino	
22		1.56E-07		Me	H	H	R7	biphenyl	R9-methoxy		amino carbonyl
23		> 1.00E-05	4.421E-07	Me	H	H	R7	biphenyl	R8-ethoxy	morpholino carbonylamino	

24		5.75E-07	> 1.000E-05	Me	H	H	R7	dibromophenyl	furylcarbonyloxy		
25		2.57E-06	6.930E-06	Me	H	H	R7	dibromophenyl	R8-ethoxy	amino	
26		> 1.00E-05	2.720E-06	Me	H	H	R7	dimethylphenyl	R8-ethoxy	tert-butoxycarbonylamino	
27		1.45E-07	> 1.000E-05	Me	H	H	R7	dimethylphenyl	R9-methoxy		2-furyl
28		3.10E-07	> 1.000E-05	Me	H	H	R7	dichlorophenyl	R9-methoxy		4-pyridinyl
29		5.37E-07	> 1.000E-05	Me	H	H	R7	dimethylphenyl	R8-ethoxy	pyrrolidinyl	

30		3.11E-07	> 1.000E-05	Me	H	H	R7	dimethylphenyl	R9-methoxy		5-methyl isoxazol-3-yl
31		4.81E-07	> 1.000E-05	Me	H	H	R7	dimethylphenyl	R8-ethoxy	diethylamino	
32		3.63E-07	> 1.000E-05	Me	H	H	R7	Br-NMe-phenyl	R9-methoxy		4-pyridinyl
33		> 1.00E-05	8.190E-08	Me	H	H	R7	2-furyl	diMe-amino		
34		> 1.00E-05	5.660E-08	Me	H	H	R7	5-Me-thiophen-2yl	diMe-amino		
35		> 1.00E-05	3.00E-08	Me	H	H	R7	biphenyl	dimethylamino		

36		4.60E-07	> 1.000E-05	Me	H	H	R7	dibromophenyl	dimethylamino
37		>e-5	4.80E-09	Me	H	H	R7	cyclopentyl	dimethylamino
38		>e-5	2.80E-08	Me	H	H	R7	isopropyl	dimethylamino
39		4.31E-06	> 1.000E-05	Me	H	H	R7	2-furyl	Furylcarbonylamino
40		> 1.00E-05	2.760E-07	Me	H	H	R7	5-Me-thiophen-2yl	prop-amino
41		> 1.00E-05	7.230E-08	Me	H	H	R7	biphenyl	Et-amino

42		2.79E-07	> 1.000E-05	Me	H	H	R7	5-Me-thiophen-2yl	R9-methylamino	4-pyridinyl
43		> 1.00E-05	3.310E-07	Me	H	H	R7	5-Me-thiophen-2yl	R9-methylamino	3-pyridinyl
44		4.53E-07	> 1.000E-05	Me	H	H	R7	dibromophenyl	isobutylamino	
45		> 1.00E-05	5.130E-08	Me	H	H	R7	biphenyl	R9-methylamino	phenyl
46		> 1.00E-05	5.290E-08	Me	H	H	R7	5-Me-thiophen-2yl	R9-methylamino	phenyl
47		1.14E-07	6.160E-08	Me	H	H	R7	dibromophenyl	R9-methylamino	3-pyridinyl

48		4.90E-08	>e-5	H	H	H	R7	dibromophenyl	dimethylamino
49		>e-5	2.90E-08	H	H	H	R7	5-bromo-2-thiophenyl	dimethylamino
50		>e-5	4.50E-08	H	H	H	R7	5-chloro-2-thiophenyl	dimethylamino